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Symptom burden and unmet needs in MPM: exploratory analyses from the RESPECT-Meso study

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ABSTRACT

Objective

Malignant Pleural Mesothelioma (MPM) has a poor prognosis and high symptom burden. RESPECT-Meso was a multicentre randomised study examining the role of early specialist palliative care (SPC) on quality of life (QoL) with MPM. This is a post-hoc exploratory analysis of the symptom burden and unmet needs identified from RESPECT-Meso participants.

Methods

Exploratory analysis from 174 participants using the General Health Status (GHS) measure (from the EORTC QLQ-C30 QoL questionnaire) and 87 participants using validated assessment questionnaires in those randomised to SPC. Eligibility for the study included confirmed MPM with diagnosis <6 weeks prior, performance score (PS) 0 or 1, no significant physical or psychological comorbidity. Cox proportional hazards models were derived to examine for relationships with survival. Free text was assessed using content analysis, looking for common themes and words.

Results:

Participants were predominantly male (79.9%), mean age 72.8 years, PS was 0 in 38%, 78% of MPM was epithelioid. At least three symptoms were reported in 69.8% of participants, including fatigue (81%), dyspnoea (73.3%), pain (61.2%), weight loss (59.3%). Anxiety was reported by 54.7% of participants, 52.3% low mood and 48.8% anhedonia symptoms. After multivariable adjustment, only pain remained statistically significant with a hazard ratio (HR) 2.9 (95% CI 1.3-6.7; p=0.01). For each 1 unit increase in GHS score, the HR for death was 0.987 (0.978-0.996; p=0.006), indicating a worse reported QoL is related to shorter survival.

Unmet needs were common: 25.9% wanted more information about their condition, 24.7% about their care and 21.2% about their treatment. 79.1% were concerned about the effect of their illness on family.

Conclusion

There is a high symptom burden in mesothelioma despite good baseline performance status. A worse QoL is associated with a worse survival. Unmet needs are common, perhaps highlighting a need for improved communication and information sharing.

INTRODUCTION

Malignant pleural mesothelioma (MPM) is an aggressive cancer arising from mesothelial cells caused by exposure to asbestos fibres. MPM has a median survival of less than 12 months [1] with the majority of individuals presenting with locally advanced disease and a high symptom burden [2-4]. Doublet chemotherapy has been shown to improve quality of life but only adds a survival benefit of a few months [5]. Newer treatments such as immunotherapy and anti-angiogenesis agents have shown promise, however results have been disappointing to date [6,7,8].

A high symptom burden can significantly impair health related quality of life (HRQoL) [2,9,10] and baseline HRQoL has been shown to be a significant independent prognostic factor across multiple tumour types including non-small cell lung cancer, colorectal cancer and mesothelioma [2,3,11-16]. Additionally, these studies have demonstrated that specific symptoms or patient-related factors may influence prognosis. Two separate meta-analyses have found that certain HRQoL parameters, such as appetite loss and pain, can provide significant prognostic value [14,15]. Furthermore, advanced cancer participants have unmet needs across a multitude of domains in addition to physical, including psychological, functional, financial and informational [9,17]. Two systematic reviews examined unmet needs across multiple cancer types and consistently found that the most prominent unmet needs were of emotional support, fatigue and inadequate information in regard to treatment [9,17].

The RESPECT-Meso study was a large multicentre randomised study examining the role of regular early specialist palliative care on the HRQoL of individuals with MPM [18]. All participants were assessed at baseline for HRQoL using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30). The participants randomised to early SPC also had further assessments at baseline – the Sheffield Profile for Assessment and Referral to Care tool (SPARC) and the Edmonton Symptom Assessment System (ESAS).

The primary outcome for RESPECT-Meso was not met as there was no statistically significant difference in HRQoL between arms. This study presents the planned exploratory analyses examining the QoL data, symptom scores and analyses of unmet needs.

METHODS

The RESPECT-Meso study design, eligibility criteria, and statistical analyses have been described in detail previously [18,19] and are summarised below.

Trial design and participants

RESPECT-Meso was a multicentre, randomised, non-blinded, parallel group-controlled trial. The trial recruited 174 participants from 19 secondary and tertiary hospitals across the UK and one tertiary hospital site in Western Australia. Potential participants were required to have Eastern Co-operative Oncology Group (ECOG) performance status of 0 to 1, a new histological or cytological diagnosis of malignant pleural mesothelioma, and able to consent in English. Participants with history of malignancy within five years, significant physical or psychiatric co-morbidity, high symptom burden at diagnosis, recent thoracic surgery or already commenced systemic anticancer therapy for mesothelioma were excluded.

Participants randomised to the intervention arm were referred to SPC within six weeks of diagnosis, regardless of perceived need and were seen every four weeks throughout the study period. Participants in the control arm received standard care, including standard referral to palliative services if indicated.

Assessment

All participants completed the EORTC QLQ-C30 at baseline (pre randomisation) and every four weeks until twenty-four weeks or drop out. The EORTC QLQ-C30 is a validated tool that incorporates functional scales including physical, cognitive and emotional, and symptom scales including fatigue, pain and nausea as well as a global health and HRQoL scale[14]. All participants were asked at baseline, twelve- and twenty-four -week clinic visits whether they reported pain.

Further, all participants randomised to the intervention arm underwent the SPARC and ESAS tools at initial consultation to ensure a standard approach to SPC. The ESAS is a short visual analogue scale across eight different symptom domains with two extra questions addressing patient-nominated “other symptoms” and location of pain [20]. SPARC is a multidimensional screening tool with 45 questions across multiple domains including communication, physical symptoms, psychological issues, religious and spiritual issues, independence, family and social issues and treatment issues.[21].

Statistical methods

Participant baseline demographic characteristics were reported using frequency and percentages for categorical data and mean and standard deviation for continuous data with a normal distribution. Exploratory analysis was performed using the General Health Status (GHS) measure derived from the EORTC QLQ-C30 QoL questionnaire. Univariate and multivariate Cox proportional hazards models were derived for the transformed GHS, physical symptom scores (reduced appetite, weight loss, pain, dyspnoea and fatigue) and composite measures of physical, psychological and social factors to examine for any relationship with survival. Spearman's rho was used to examine correlation between the measures.

Survival was analysed using a joint modelling approach with QoL, incorporating outcome measurements at various time points and survival time, with surviving participants censored at their 24-week visit or date of last visit if they dropped out earlier than 24 weeks. Results of the ESAS and SPARC were reported using frequency and percentages for categorical data. Correlation between ESAS and SPARC common domains were assessed using Pearson's Chi test. Free text was assessed using content analysis, looking for common themes and words. Statistical analyses were performed using Stata V.15.1 (StataCorp LP, College Station, TX, USA). Additional figures were produced using the Bioinformatics and Evolutionary Genomics Venn diagram tool (Ghent University, Gent, BELGIUM).

RESULTS

The RESPECT-Meso study randomised 174 participants, 87 to each arm with exploratory analysis in the intention-to-treat (ITT) population. The median follow-up time was 41.1 weeks (range 2-133 weeks). Baseline demographic and clinical characteristics of both study arms were well matched and are presented in table 1. The baseline EORTC QLQ C30 was completed by 173 participants; 147 at 12 weeks, and 125 participants at 24 weeks. Eighty-seven participants were allocated to the early SPC and 86 participants completed the SPARC and ESAS assessments.

Mean (SD) baseline GHS score in the standard care arm was 66.9 (22.6) and in the intervention arm was 66.1 (20.0). From the QLC-C30, dyspnoea was reported as 'quite/very much' by 53/173 (30.6%) participants, pain 'quite/very much' by 40/170 (23.5%) and fatigue 'quite/very much' by 47/172 (27.3%).

Physical symptoms

The three most common symptoms on the EORTC QLQ-C30 were pain (n=40, 24%), dyspnoea (n=53, 31%) and fatigue (n=47, 27%). The reported symptom burden was similar between treatment groups at all time points and did not change significantly over time (data not presented).

Using the ESAS tool, n=84 (97.7%) participants presented with at least 1 symptom and n=60 (69.8%) with 3 or more symptoms. The frequency and severity of symptoms are shown in figure 1. The most common symptom reported was fatigue (n=70, 81.4%), followed by dyspnoea (n=63, 73%) and pain (n=52, 60%). On content analysis of the "other" symptoms (n=13), the most common was constipation (n=7) with other complaints including bladder incontinence (n=1), frustration (n=1), confusion (n=1), cold sores (n=1), diarrhoea (n=1) and dysphagia (n=1). The responses to the ESAS by symptoms are presented in figure 1.

Using the SPARC tool, 86 participants reported a median of 9 symptoms (range 0-18) of the 22 physical symptoms interrogated. Dyspnoea (n=75, 87%), fatigue (n=74, 86%) and pain (n=65, 76%) were the most commonly reported symptoms. Dyspnoea was also the most common symptom reported as "very much" (n=10).

There was no difference in reporting of the common symptoms between the ESAS and SPARC. The total ESAS and SPARC scores demonstrated a strong correlation with GHS (R^2=0.2; $p<0.01$ and R^2=0.3; $p<0.01$ respectively).

Pain

For all participants, 100 of 174 (57%) reported pain at baseline, 84 of 154 (55%) at 12 weeks and 74 of 127 (58%) at 24 weeks, (p value for trend 0.79). In the intervention arm, 52 participants (59.7%) reported pain on the ESAS scale, but only 46 participants (53%) marked a location of pain on the diagram or wrote in their location of pain. Of the 46 participants that identified a location of pain, most participants noted multiple sites of pain with a total of 70 locations of pain. 35 (50%) participants reported pain in the chest or chest wall region, with 23 (33%) reporting back pain and 12 (17%) reporting pain elsewhere.

Quality of life, symptoms and survival

Overall survival was assessed in relation to the three most common physical symptoms: dyspnoea, pain and fatigue. For all three symptoms, the estimated median survival times were higher in the low severity category and the log rank test suggested significant differences in survival between participants with high and low symptom severity (see table 2). The estimated HR for both dyspnoea and pain was 1.7 (95% CI: 1.1-2.6) i.e. the hazard for death was 70% higher in those in the high severity group. The HR for fatigue was 1.9 (95% CI: 1.3-3.0).

For each 1 unit increase in GHS score, the estimated hazard ratio (HR) for death was 0.987 (95% CI: 0.978, 0.996), p=0.006. Figure 2 demonstrates the relationship of GHS with survival for all participants, suggesting a higher baseline HRQoL is associated with a longer survival. The univariable HR (for death) of reduced appetite was 2.3 (95% CI 1.2-4.4; p=0.01); loss of weight 1.8 (0.98-3.4; p=0.06); dyspnoea 1.9 (1.1-3.5; p=0.03); pain 1.5 (0.8-2.9; p=0.19); and fatigue 2.5 (1.4-4.4; p=0.003). After multivariable adjustment for age, gender, PS, chemotherapy, sarcomatoid containing histology, comorbidities and baseline GHS, only pain remained statistically significant with a HR 2.9 (1.3-6.7; p=0.01).

Communication and information

Participants stated that they were able to discuss their condition with their doctor (n=61/87), community nurses (n=22), hospital/specialist nurses (n=65) and family (n=82). In the free text, 34 participants (40%) reported discussing with friends and 7 participants reporting discussion with asbestos/mesothelioma support groups. Religious support was sought by 7 participants, 6 participants spoke with a social worker, 1 to a clinical psychologist, and 1 with hospice staff. Figure 3 demonstrates the interrelationship of whom the participants were able to discuss their condition with.

With regard to the areas of concern for participants, 34 (40%) participants were concerned about the side effects of treatment. Thirty-three (38%) participants were concerned about the long-term effects of treatment. Twenty-two (26%) participants were concerned about both. Participants felt that they needed more information about their condition (n=22) and care (n=21). In the free text section of more information or questions, 29 participants wrote that they required more information about prognosis and palliative care/end of life care (n=14), treatment (n=10), symptoms (n=10) and diagnosis (n=5). Of those asking about diagnosis, 1 requested a second opinion to confirm diagnosis, 2 were unsure of extent of disease and 2 were frustrated and angry at delays in diagnosis.

Psychological and Spiritual needs

Anxiety was among the most common psychological symptom from the SPARC questionnaire with 47 out of 86 (55%) responses, although of these, most participants reported a low level of severity in anxiety (n=35, "a little bit"). Low mood (n=45, 52%), feeling like "everything is an effort" (n=42, 49%) and inability to concentrate (n=36, 42%) were the next most common symptoms. Only 4 participants reported high levels ("very much") of psychological symptoms – these were low mood (n=1) and effect on sex life (n=3). 29 (34%) participants reported worrying about death and dying. Only 2 participants reported inadequate needs met in terms of religious or spiritual support.

Independence and Support/Family

Most participants were concerned about the impact of their disease on family (n=68). Only 11 participants reported being concerned about their support network being unable to care adequately for them. 32 participants reported fears about losing independence, 36 participants reported concerns about losing ability to perform activities of daily living (ADLS), and 20 reported concerns about performing household tasks. Few participants reported concerns about personal affairs (n=7) or requested an alternative opinion about their care (n=9).

DISCUSSION

This study demonstrates the considerable symptom burden, the influence of symptoms on HRQoL and the prognostic importance of HRQoL in relatively fit individuals, early in the disease course with MPM. Furthermore, individuals with MPM are seeking information from a wide support network, highlighting potentially important unmet needs.

Despite the design of this study only including participants with good performance status (0 or 1), within the intervention arm, approximately 70% of participants presented with 3 or more symptoms, with 62% reporting a moderate to high severity of those symptoms. This is similar to other studies, which found that a third of all patients diagnosed with cancer, regardless of stage, had two or more symptoms[22]. The most common symptoms in this study were dyspnoea, pain and fatigue. The presence of dyspnoea, pain, anorexia, fatigue and/or weight loss was associated with a statistically significant difference in survival in univariable analysis.

After adjustment for multiple clinical variables only the presence of pain remained statistically significant with a HR for death of 2.9 (95% CI 1.3-6.7; p=0.01). This is consistent with other studies and pain is recognised as a

prognostic factor across many tumour types [12,14,15]. Pain has a direct impact on HRQoL and perhaps disease outcomes, with theories about the release of tachykinins that may modulate immune function, or cause cyclo-oxygenase mediated prostaglandin release [23,24]. Additionally, the psychological impact of cancer pain is well established, with known links to significant psychological and physical impairment [25]. The presence of pain has been significantly associated with depressive and anxiety symptoms in addition to poor overall quality of life and dissatisfaction with health care [25,26]. Pain at presentation, even in patients with good performance status, could therefore be a trigger for consideration of referral to palliative care not only because of symptom burden, but because a quarter of patients had questions about prognosis or end of life care. These patients are likely to have a shorter survival and thus are likely to benefit from earlier opportunities for such advance care planning [27].

Fatigue was also a prominent physical symptom in our study, in common with other reports [28,29]. It is a key physical symptom predictive of survival and an established unmet need within the cancer population [9,17]. Fatigue is common, with up to 86% of participants in the intervention arm of our study reporting such (from the SPARC tool), and at least 27% reporting "tiredness" in the overall cohort (from the QLQ-C30). This is consistent with other studies, reporting rates between 61-94% [2,29]. Fatigue is a difficult symptom to manage and is perhaps related to pro-inflammatory cytokines which are themselves related to the neutrophil-lymphocyte-ratio and vascular endothelial growth factor [16]. The impact of fatigue is greater than simply feeling tired as it impacts on both social and physical function, and functional independence [30].

The social impact of a new diagnosis of MPM cannot be underestimated. A cancer diagnosis can lead to change in identity, role within the family unit, relationships and in some cases leads to social isolation[10]. There is often fear about becoming a burden to their families which is common in all cancer types[9,17]. This study confirms this for MPM patients, with 79.1% of participants worried about the effect of their illness on their families, and 12.8% concerned that they might need more support than their family can provide. Participants were fearful of losing their independence (37.2%) and their ability to perform ADLs (23.3%) or household tasks (41.9%). Participants also turned to support outside their families, with 40% of participants identifying friends, including neighbours and work colleagues, as people they felt they could communicate their diagnosis with. Collectively, these data have a simple message, many patients with MPM (and their families) may need more support soon after the diagnosis and patients are fearful of impact on their families.

Most participants (65 of 87, 75%) had the opportunity to discuss their diagnosis and care with specialist nurses. The high proportion of participants reporting discussions with specialised thoracic nurses is likely a reflection of the recruiting specialist centres, all which had senior specialised thoracic cancer nurses, who play a key role in the early care and diagnosis of cancer patients [31,32]. MPM is frequently associated with occupational exposure and thus there are often medicolegal and compensation implications to the diagnosis. Therefore, it is noteworthy that just seven participants mentioned seeking support from asbestos disease/mesothelioma support groups. This study may be either under reported, under-utilised or may reflect inadequate resourcing and represent an educational need for thoracic cancer nurses.

This study demonstrated that for each unit increase in GHS (HRQoL) score, survival improved (HR for death 0.987 (95% CI: 0.978 to 0.996), p=0.006). These results are consistent with other reports using other measures, Hollen *et al* [2], used the Lung Cancer Symptom Scale modified for mesothelioma (LCSS-Meso) tool to assess HRQoL and found that poor baseline overall QoL scores were associated with a shorter survival time, with loss of appetite and pain being significant predictors of survival. Nowak *et al* [3], found that baseline scores from the EORTC QLQ-C30 and lung cancer module-13 were significant predictors of survival, with fatigue and physical function being the strongest predictors. Kao *et al* [16], found a similar constellation of symptoms using LCSS-Meso statistically significant for survival on multivariate analysis.

As HRQoL is a reflection of physical, social and mental health, future work to address any modifiable aspects that influence QoL is required. For instance, this study highlights the unmet education and support needs of many patients with MPM (and their families) soon after the diagnosis of MPM, suggesting that improvements in clinical and support services may be required. Further trials such as the ANTHEM study, which will examine the efficacy of a Ghrelin agonist to treat weight loss and poor appetite in patients with MPM [33] are required to address modifiable physical symptoms. Finally, this study found that there is a good correlation between the different HRQoL measures that were used, which suggests it does not matter exactly which measure is used in this population, so long as a measure of QoL is used.

Potential limitations should be considered when interpreting the data from this study, particularly, that of generalisability. Our study population was selected for their relatively good performance status and thus is not

necessarily reflective of the wider population with MPM. Nevertheless, 108 (59%) of those recruited had a PS of 1 and the median survival for all participants was just 52 weeks, consistent with the expected survival of MPM[1]. Presumably, individuals with a worse PS at MPM diagnosis will have a higher burden of the same physical, psychological and emotional symptoms as well as unmet needs. These patients should be flagged as having a poor prognosis using simple decision tools [34]to allow their primary carers to access relevant support in advanced care planning and end of life care strategies.

Conclusion

This study demonstrates that patients with mesothelioma have a high burden of symptoms, even at an early stage. Increasing physical symptoms and lower quality of life scores are associated with poor survival. Unmet needs are common and wide support networks are utilised to support mesothelioma patients and their families.

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Table 1. Baseline characteristics

	Standard Care (N=87)		**Regular Early SPC (N=87)**	
Numbers included	n		n	
Age *Mean (SD)*	87	73.2 (8.2)	87	72.4 (7.8)
Gender *Male (%)*	87	72 (82.8)	87	67 (77.0)
Histological subtype *Non-Epitheliod/Epitheliod* *(% Non-Epitheliod/Epitheliod)*	87	19/68 (21.8/78.2)	87	19/68 (21.8/78.2)
Plan for chemotherapy *Yes (%)*	86	45 (52.3)	87	47 (54.0)
ECOG performance status *0/1* *(% 0/1)*	87	32/55 (36.8/63.2)	87	34/53 (39.1/60.9)

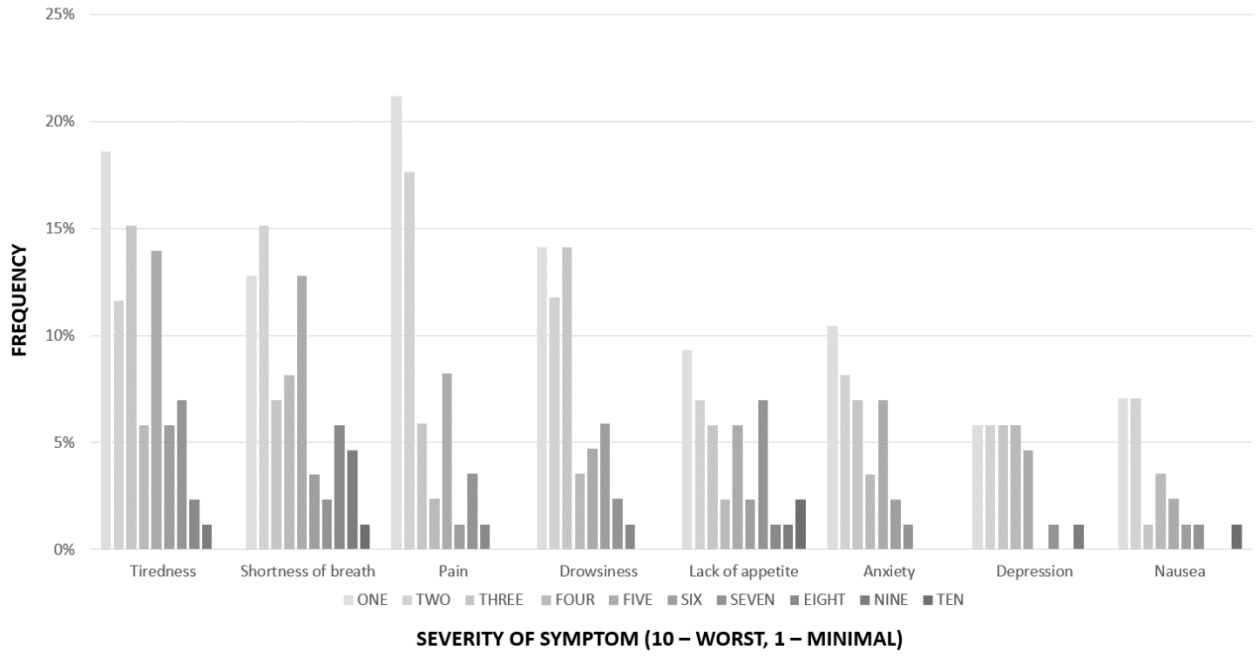
SD – standard deviation; ECOG – Eastern Co-operative Oncology Group

Table 2 - The relationship of the three most commonly reported symptoms mesothelioma and outcome.

Reported symptoms from QLQ-C30	**Dyspnoea**		**Pain**		**Fatigue**	
	No/a little	*quite/very much*	*No/a little*	*quite/very much*	*No/a little*	*quite/very much*
Number of deaths (%)	59 (49.2)	34 (64.2)	66 (50.8)	26 (65.0)	60 (48.0)	32 (68.1)
Median survival time in weeks (95% CI)	65.3 (49.1, 78.3)	41.0 (28.1, 69.0)	59.4 (46.4, 77.6)	45.1 (22.4, 67.3)	67.3 (49.3, 78.3)	42.7 (24.0, 54.7)
Log rank test	0.01		0.03		0.002	
Hazard ratio (95% CI)	1.7 (1.1-2.6)		1.7 (1.1-2.6)		1.9 (1.3-3.0)	
P-value (Cox PH)	0.02		0.03		0.003	

QLQ-C30 - European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; CI – confidence interval

Figure 1– Edmonton Symptom Assessment System (ESAS); symptoms by severity (graph) and frequency (table) (N=86)



Number of symptoms on presentation as reported by ESAS (n)	0	1	2	3	4	5	6	7	8	9	10
Frequency (total = 86)	2	7	5	12	6	13	17	14	1	7	2
Percentage of patients presenting with at least (n) number of symptoms	-	98%	90%	84%	70%	63%	48%	28%	12%	10%	2%

Figure 2. The relationship of baseline reported quality of life and survival

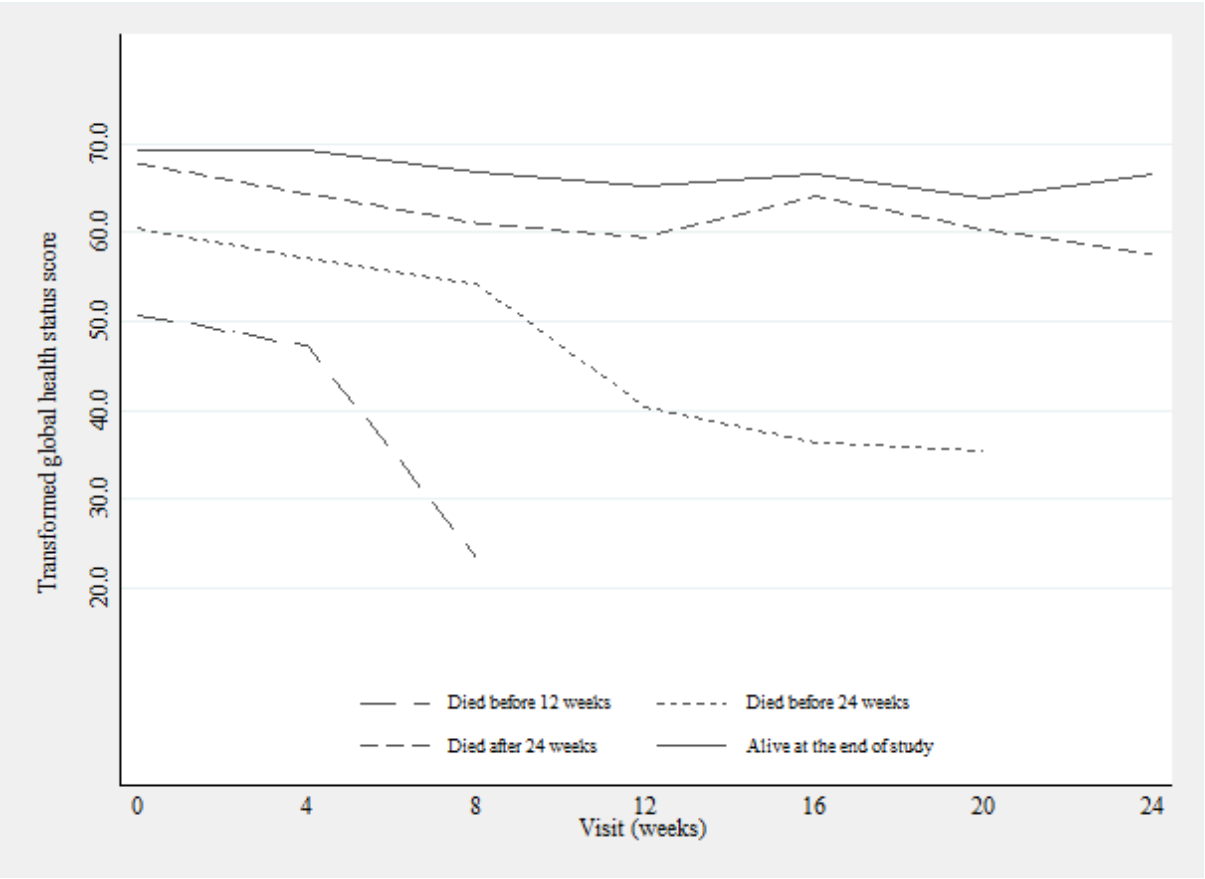


Figure 3 - The interrelationship of reported support networks for mesothelioma patients (from the five largest groups)